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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-2904

January 5, 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Patrick J. Zenner, President and CEO
Hoffmann-LaRoche, Inc.
340 Kingsland Street
Nutley, New Jersey 07110

RELEASE
RELEASED BY AC 11/14/98
C.O. DATE

FILE NO.: 98-NWJ-02

Dear Mr. Zenner:

During the period of May 13 through June 3, 1997 and on August 27, 1997, investigators from the New Jersey District Office conducted inspections at your facility located at 340 Kingsland Street, Nutley, N.J., to determine your firm's compliance with the Postmarketing Adverse Drug Experience (ADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act), and Title 21 Code of Federal Regulations Part 314.80.

Based on our review of the inspection reports, we conclude that your firm failed to comply with Section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.80 which requires the reporting of data relating to clinical experience for drugs for which an approval of an application filed under Section 505(b) (1) is in effect.

Deviations from ADE regulations include:

1. The firm did not submit a number of Adverse Drug Experience (ADE) reports that were both serious and unexpected within 15 working days as required by the regulations (21 CFR 314.80(c)(1)). Some reports were not submitted for months; some exceeded years. Some of these late reports were not submitted until after the inspection was concluded.

Examples of late reports include:

Product	[redacted]	Date received by Manufacturer	Date Sent to FDA
Bactrim		6/03/92	10/08/97
Lariam Tabs		7/09/96	10/08/97
Lariam Tabs		8/28/90	10/08/97
Lariam Tabs		10/05/90	10/08/97
Roaccutane oral		10/31/91	10/08/97
Roaccutane oral		9/04/91	10/08/97
Tigason oral		7/24/91	10/08/97
Rocephin Inj.		11/04/86	10/08/97
Rocephin Inj.		3/03/95	10/08/97
Rocephin Inj.		12/31/90	4/19/95
Amitriptyline oral		7/29/91	11/28/95
Rocephin Inj.		11/08/91	11/27/95
		6/20/86	11/04/94

These are only limited examples, and as we observed by the widespread origin of these reports, i.e., domestic and foreign, including France, Japan, and Australia, appear to be indicative of systems deficiencies in handling ADE reporting.

2. The date on which initial ADE information was obtained by the manufacturer was incorrectly documented on the Medwatch Form. Examples include:

Product	[redacted]	Actual Date	Date on Medwatch
Ticlid oral (USA)		3/29/96	4/16/96
Invirase oral (USA)		8/15/96	8/30/96
Fluorouracil I.V. (USA)		3/17/97	10/23/96

As a result of these miscodings, the 15 day reports were also submitted late to the agency.

We have reviewed your response letter dated June 20, 1997, regarding the inspectional observations listed on the FD-483 and the letters from Dr. Alan Bess, Vice President, Drug Safety, dated September 8, 1997. We note that in these letters Dr. Bess states that your firm is confident that the processing of adverse drug event reports is functioning efficiently, that all French reports are now processed in a timely manner and that your firm is taking further action to improve the ADE reporting.

We acknowledge that your firm has initiated corrective actions. We note, however, that as recently as October 8, 1997, your firm submitted late reports (with some going back to 1989) which had not been previously reported. We ask that you reply to this Warning Letter, being specific as to what steps have been taken to assure that all required reports have now been submitted and that the reporting deviations will not occur again. If you have not completed corrective actions, please provide a time table for completion of all corrective actions, including the implementation of system changes. Your response should address ADE reporting from all domestic and foreign facilities. We will confirm the adequacy of the corrections during subsequent inspections.

FDA expects drug manufacturers to establish reasonable mechanisms to assure that their foreign affiliates rapidly transmit information to allow for expedited reporting of serious, unlabeled adverse drug experiences.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Act and its regulations. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include but are not limited to seizure and/or injunction.

We request that you reply in writing within 15 working days of receipt of this letter. Your reply should be sent to the U.S. Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attention: Andrew Ciaccia, Compliance Officer. We will be contacting you to schedule a suitable date and time for a meeting at our district office to discuss the inspectional findings and corrective actions being taken by your firm.

Sincerely,

Douglas I. Ellsworth

Douglas I. Ellsworth
District Director
New Jersey District Office

AC:slw